Claim 15 has been amended to correct a typographical error by deleting "g is the integer 1, 2, 3 or 4". No new matter has been added. Claim 26 has also been amended to correct a typographical error by replacing the terms "α4β1" and "α4β1" with the terms "$\alpha_4\beta_1$" and "$\alpha_4\beta_1$." No new matter has been added.

I. Alleged Indefiniteness

A. Claims 1 to 18 and 20 to 26 have been rejected under 35 U.S.C. § 112, second paragraph because the phrase "linker atom or group" is allegedly indefinite. Without conceding the correctness of the rejection, and to advance prosecution, claim 1 has been amended to delete the cited phrase and to further clarify the definitions of L^3, L^4, and L^1. Support for the amendment is found in the specification at, for example, page 8, lines 12 to 20 and page 14, lines 9 to 11. The rejection has been rendered moot, and Applicants respectfully request withdrawal thereof.

B. Claims 1, 2, 5 to 18, and 20 to 26 have been rejected under 35 U.S.C. § 112, second paragraph as indefinite because the structures of the carboxylic acid derivatives allegedly cannot be determined. Without conceding the correctness of the rejection, and to advance prosecution, claim 1 has been amended to delete the term "derivative" and to recite carboxylic acid esters and carboxylic acid amides. Support for the amendment is found in the specification at, for example, page 11, lines 20 to 24. The rejection has been obviated, and Applicants respectfully request withdrawal thereof.

C. The Office Action also asserts[1] that the phrase "biostere thereof" is indefinite because it is allegedly unclear what is encompassed by the phrase. Applicants respectfully traverse the rejection because the term "biostere" is readily understood by those of ordinary skill in the art.

"The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 [second paragraph] demands no more." *Miles Laboratories, Inc. v. Shandon Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993). If a skilled artisan can determine whether a particular chemical compound is or is not within the scope of a claim, the requirement of § 112, second paragraph has been fulfilled. *In re Miller*, 441 F.2d 689, 692 (C.C.P.A. 1971).

Definiteness of claim language must be analyzed, not in a vacuum, but in light of the content of the particular application disclosure, the teachings of the prior art, and the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. *In re Moore*, 439 F.2d 1232, 1235 (C.C.P.A. 1971); M.P.E.P. § 2173.02. When the present claim language is so examined, it is apparent that the meaning of the term "biostere thereof" would be readily understood by those of ordinary skill in the art. For example, examination of the instant disclosure reveals that examples of carboxylic acid biosteres are provided. (See, for example, page 11, lines 23 to 26 of the specification as filed.). Furthermore, carboxylic acid biosteres are well known in the art. For example, the textbook *The Practice of Medicinal Chemistry* (excerpt attached

[1] The Office Action has not made the assertion in the context of a rejection of specified claims. If the rejection is maintained, Applicants respectfully request the Examiner to specify which claims have been rejected on this basis.

hereto as Appendix A) defines the term "bioisosteres," for which "biostere" is an abbreviation, and provides a detailed description of carboxylic acid biosteres, and lists numerous examples of carboxylic acid biosteres. (The Practice of Medicinal Chemistry, Camille G. Wermuth, editor, Academic Press, 1996, pages 204 to 208 and 215-216).

Carboxylic acid biosteres, therefore, are described in the specification and are well-recognized in the art of organic chemistry. Those of ordinary skill in the art would understand which groups are encompassed by the phrase "biostere thereof," and would not have any difficulty determining whether a particular compound falls within the scope of the claims. The requirements of the second paragraph of 35 U.S.C. § 112 have therefore been met, and Applicants accordingly request withdrawal of the rejection.

D. Claims 1 to 12, 14 to 18, and 20 to 26 have been rejected under 35 U.S.C. § 112, second paragraph as indefinite for recitation of the terms "cycloaliphatic," "heterocycloaliphatic," "polycycloaliphatic," and "heteropolycycloaliphatic" because the terms are allegedly oxymorons and the subject matter encompassed by the terms is allegedly unclear. Without conceding the correctness of the rejection, and to advance prosecution, claims 1 and 12 have been amended to further clarify the claimed subject matter. Specifically, claim 1 has been amended to replace the term "cycloaliphatic" with the terms "C_{3-10}cycloalkyl" and "C_{3-10}cycloalkenyl." Support for the amendment is found in the specification at, for example, page 15, lines 17 to 21. Claim 1 has also been amended to replace the term "heterocycloaliphatic" with the terms "C_{3-10}heterocycloalky" and "C_{3-10}heterocycloalkenyl." Support for the amendment is found in the specification at, for example, page 15, lines 23 to 28. Claim 1 has also been amended to replace the term "polycycloaliphatic" with the terms "C_{7-10}bicycloalkyl," "C_{7-10}tricycloalkyl," "C_{7-}

$_{10}$bicycloalkenyl," and "C_{7-10}tricycloalkenyl." Support for the amendment is found in the specification at, for example, page 15, lines 30 to 33. Claim 1 has also been amended to replace the term "heteropolycyclo-aliphatic" with the terms "C_{7-10}bicycloheteroalkyl," "C_{7-10}tricycloheteroalkyl," "C_{7-10}bicycloheteroalkenyl," and "C_{7-10}tricycloheteroalkenyl." Support for the amendment is found in the specification at, for example, page 15, lines 33 to 35. Finally, claim 1 has been amended to recite that the heteroaliphatic, heterocycloalkyl, heterocycloalkenyl, bicycloheteroalkyl, tricycloheteroalkyl, bicycloheteroalkenyl and tricycloheteroalkenyl groups contain one, two, three, or four heteroatoms or heteroatom-containing groups as defined for L^3 and L^4, which may be the same or different. Support for the amendment is found in the specification as filed at, for example, page 15, lines 17 to 28, page 14, line 27 to page 15, line 2, and page 8, lines 12 to 20.

In addition, claim 12 has been amended to replace the term "C_{5-7}heterocycloaliphatic" with the terms "C_{5-7}heterocycloalkyl" and "C_{5-7}heterocycloalkenyl." Support for the amendment is found in the specification at, for example, page 15, lines 23 to 28. The rejection has been obviated, and Applicants respectfully request withdrawal thereof.

E. Claim 19 has been rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for recitation of the term "particularly." Without conceding the correctness of the rejection, and to advance prosecution by further clarifying the claimed subject matter, claim 19 has been amended to delete the phrase "particularly the methyl, ethyl, propyl and i-propyl esters thereof." New dependent claim 27 recites a compound according to claim 19 wherein the carboxylic acid esters are selected from the group consisting of methyl, ethyl, propyl, and i-propyl. Support for new claim 27 is found in claim

19 as originally filed. The rejection has been obviated, and Applicants respectfully request withdrawal thereof.

F. Claim 21 has been rejected under 35 U.S.C. § 112, second paragraph as indefinite because it is allegedly unclear from the phrase "treatment of...a disease or disorder in a mammal in which the extravasation of leukocytes plays a role" what treatments are being claimed. (Office Action dated July 24, 2002, page 5). Without conceding the correctness of the rejection, and to advance prosecution by further clarifying the claimed subject matter, claim 21 has been amended to replace the cited phrase with a recitation of exemplary diseases and disorders. Support for the amendment is found in the specification at, for example, page 28, line 31 to page 29, line 5. The rejection has been obviated, and Applicants respectfully request withdrawal thereof.

G. Claims 22 to 24 have been rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite because they are method claims, but depend from a compound claim. Without conceding the correctness of the rejection, and to advance prosecution by further clarifying the claimed subject matter, claim 21 has been amended to recite a method, rather than a compound. Claim 22 has been cancelled, and claims 23 and 24 have been amended to depend from claim 21. Support for the amendments is found in the specification at, for example, page 28, line 31 to page 29, line 5. The rejection has been obviated, and Applicants respectfully request withdrawal thereof.

II. Alleged Lack of Enablement

A. Claims 1 to 27 have been rejected under 35 U.S.C. § 112, first paragraph because the specification allegedly fails to enable those of skill in the art to make solvates or

hydrates of the claimed compounds without undue experimentation. Applicants respectfully traverse the rejection because those of skill in the art could readily make solvates or hydrates of the claimed compounds.

The enablement requirement is met if the specification enables those of ordinary skill in the art to make and use the subject matter defined by the claims without undue experimentation. *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976). The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, whether it is undue. *Id.* Extensive experimentation is often necessary to practice inventions that involve unpredictable technologies, and such experimentation is not undue if the art typically engages in such experimentation. *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

As known to those of ordinary skill in the art, a solvate is a complex of molecules or ions of a solvent with those of a solute. See, *e.g.*, Grant & Hack's Chemical Dictionary, Fifth Ed., McGraw-Hill, Inc., p. 542 (1987) (attached herewith at Appendix B). In addition, as also known to those of ordinary skill in the art, a hydrate is a substance containing water combined in the molecular form. See, *e.g.*, Grant & Hack's Chemical Dictionary, Fifth Ed., McGraw-Hill, Inc., p. 289 (1987) (attached herewith as Appendix C). Processes for preparing solvates and hydrates of organic compounds are well known to those of skill in the art, and can be found in standard organic chemistry reference books. Accordingly, it is respectfully submitted that undue experimentation would not be required to make solvates or hydrates of the compounds defined by the present claims. Accordingly, Applicants respectfully request withdrawal of the rejection.

B. Claims 21 to 24 have been rejected under 35 U.S.C. § 112, first paragraph for lack of enablement because the specification allegedly fails to enable the prophylaxis "of any disease." (Office Action dated July 24, 2002, page 6). Without conceding the correctness of the rejection, and to advance prosecution by further clarifying the claimed subject matter, claim 21 has been amended to delete the word "prophylaxis." Support for the amendment is found in the specification at, for example, page 28, line 31 to page 29, line 5. The rejection has been obviated, and Applicants respectfully request withdrawal thereof.

C. Claims 21 and 22 have been rejected under 35 U.S.C. § 112, first paragraph because the specification allegedly fails to enable those of skill in the art to treat multiple sclerosis with the claimed α4 integrin inhibitors. Applicants respectfully traverse the rejection.

The Office Action has cited numerous references in support of the proposition that "[c]ell adhesion inhibitors are not presently art-recognized to be efficacious for [treatment of multiple sclerosis]." (Office Action dated July 24, 2002, page 8). Applicants respectfully direct the Examiner to the attached Drug Report (attached herewith as Appendix D) describing a humanized monoclonal antibody that acts as a specific inhibitor of the α4β1 integrin VLA4, which is currently in Phase III clinical trials for the treatment of multiple sclerosis. In addition, Applicants also direct the Examiner to the attached chapters from *Cell Adhesion Molecules and Matrix Proteins – Role in Health and Diseases*, S.A. Mouse (editor), Springer, 1998 ("the Mouse excerpt") (attached herewith at Appendix E). The Mouse excerpt indicates that inhibition of VLA4 in animal models of multiple sclerosis (known as experimental autoimmune encephalomyelitis or EAE) using anti-α4 integrin monoclonal antibodies is effective in attenuating signs of paralysis and suppressing mononuclear cell

infiltration into CNS tissue. See pages 140 to 142. Alpha4 integrin inhibitors have therefore been shown to be effective for the treatment of multiple sclerosis in animal models ***and*** in clinical studies performed on humans. Thus, in contrast to the assertion made in the Office Action, cell adhesion inhibitors, specifically α4 integrin inhibitors, ***are*** recognized in the art as efficacious for the treatment of multiple sclerosis. Accordingly, as the rejection appears to be based on the alleged lack of recognition in the art of the effectiveness of cell adhesion inhibitors for the treatment of multiple sclerosis, Applicants respectfully request withdrawal thereof.

D. Claims 25 and 26 have been rejected under 35 U.S.C. § 112, first paragraph for lack of enablement because the claims allegedly read on "α4 integrin binding inhibition in mammals with below normal α4 integrin binding activity, α4 integrin binding inhibition in mammals with normal α4 integrin binding activity, or in asymptomatic mammals with up-regulated α4 integrin binding activity [and] [t]he specification fails to teach any benefit to be gained from such actions." (Office Action dated July 24, 2002, page 9). Without conceding the correctness of the rejection, and to advance prosecution by further clarifying the claimed subject matter, claim 25 has been amended to recite a method of inhibiting, in a mammal suffering from a disease or disorder associated with above-normal α4 integrin activity, the binding of α4 integrins to the ligand thereof. Support for the amendment is found in the specification at, for example, page 28, line 25 to page 29, line 5. The rejection has been obviated, and Applicants respectfully request withdrawal thereof.

III. Alleged Lack of Written Description

Claim 21 has been rejected under 35 U.S.C. § 112, first paragraph for lack of written description because the specification allegedly fails to describe diseases or disorders in which the extravasation of leukocytes plays a role. Applicants respectfully submit that the specification describes and lists numerous examples of such diseases and disorders. (See page 28, line 31 to page 29, line 5 of the specification as filed). Nevertheless, to advance prosecution, claim 21 has been amended to replace the phrase "a disease or disorder in a mammal in which the extravasation of leukocytes plays a role" with a recitation of such diseases and disorders. Support for the amendment is found in the specification at, for example, page 28, line 31 to page 29, line 5. The rejection has been obviated, and Applicants respectfully request withdrawal thereof.

IV. Alleged Double Patenting

Claims 1 to 14 and 20 to 26 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1, 3 to 6, 9, and 10 of copending U.S. Patent Application No. 09/579,317. In addition, claims 1 to 26 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over the claims of copending U.S. Patent Application No. 09/742,038. Applicants request deferral of these rejections pending the identification of allowable subject matter in the present application, as they likely can be readily resolved (depending upon the subject matter ultimately allowed) through the filing of a suitable terminal disclaimer.

V. Copending U.S. Applications and Patents

Applicants would like to bring the following co-pending United States patent applications, which relate to VLA-4 inhibitors, to the attention of the Examiner. Applicants do not concede that the applications are material to the patentability of the present application.

Serial Number	Filing Date
09/258,522	February 26, 1999
09/274,918	March 23, 1998
09/326,020	June 4, 1999
09/408,243	September 29, 1999
09/450,999	November 29, 1999
09/579,317	May 25, 2000
09/899,488	July 5, 2001
09/835,656	April 16, 2001
09/867,016	May 29, 2001
09/947,107	September 5, 2001
09/994,411	November 27, 2001
10/081,072	February 22, 2002

In addition, Applicants would like to bring the following United States patents, which relate to VLA-4 inhibitors, to the attention of the Examiner. Applicants do not concede that the patents are material to the patentability of the present application.

Patent Number
6,093,696

6,197,794

6,329,372

6,329,362

6,465,471

6,110,945

6,369,229

6,362,204

6,274,577

6,348,436

6,455,539

6,403,608

6,469,025

Application number 09/579,317 and patent number 6,455,539 relate to squaric acid derivatives.

A Supplemental Information Disclosure Statement and accompanying 1449 Form are being filed separately with the Patent Office in which each of the foregoing patent applications and patents are cited.

Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the Office Action of record. Accordingly, an early and favorable Action is respectfully requested.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Respectfully submitted,

Jane Inglese

Date: December 18, 2002

Jane E. Inglese, Ph.D.
Registration No. **48,444**

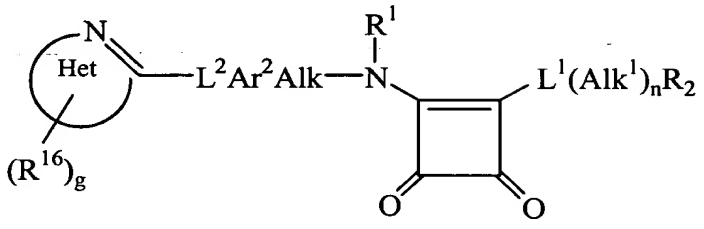
WOODCOCK WASHBURN LLP
One Liberty Place - 46th Floor
Philadelphia, PA 19103
(215) 568-3100

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

The claims have been amended as follows.

1. (Amended) A compound of formula (1):



(1)

wherein

Het is a bicyclic fused ring heteroaromatic group;

g is zero or the integer 1, 2, 3 or 4;

Each R^{16}, which may be the same or different, is an atom or group $-L^3(Alk^2)_tL^4(R^4)_u$, ~~which~~ L^3 and L^4, which may be the same or different, ~~is~~ are each a covalent bond or a linker atom or group -O-, -S-, -C(O)-, -C(O)O-, -OC(O)-, -C(S)-, -S(O)-, $-S(O)_2-$, $-N(R^8)-$, $-N(R^8)O-$, $-N(R^8)N-$, $-CON(R^8)-$, $-OC(O)N(R^8)-$, $-CSN(R^8)-$, $-N(R^8)CO-$, $-N(R^8)C(O)O-$, $-N(R^8)CS-$, $-S(O)_2N(R^8)-$, $-N(R^8)S(O)_2-$, $-N(R^8)CON(R^8)-$, $-N(R^8)CSN(R^8)-$, or $-N(R^8)SO_2N(R^8)-$,

R^8 is is a hydrogen atom or an optionally substituted C_{1-6}alkyl group,

t is zero or the integer 1,

u is an integer 1, 2 or 3,

Alk^2 is an aliphatic or heteroaliphatic chain, ~~and~~

R^4 is a hydrogen or halogen atom or a group selected from an optionally substituted C_{1-6}alkyl or C_{3-8} cycloalkyl group, $-OR^5$ ~~[~~(where R^5 is a hydrogen atom, an optionally substituted C_{1-6}alkyl or C_{3-8} cycloalkyl group)~~]~~, $-SR^5$, $-NR^5R^6$ ~~[~~(where R^6 is as just defined for R^5 and may be the same or different)~~]~~, $-NO_2$, -CN, $-CO_2R^5$, $-SO_3H$, $-SOR^5$, SO_2R^5, $-SO_3R^5$, $-OCO_2R^5$, $-CONR^5R^6$, $-OCONR^5R^6$, $-CSNR^5R^6$, $-COR^5$, $-OCOR^5$, $-N(R^5)COR^6$, $-N(R^5)CSR^6$, $-SO_2N(R^5)(R^6)$, $-N(R^5)SO_2R^6$, $N(R^5)CON(R^6)(R^7)$ ~~[~~(where R^7 is a hydrogen atom, an optionally substituted C_{1-6}alkyl or C_{3-8}cycloalkyl group)~~]~~, $-N(R^5)CSN(R^6)(R^7)$ or $-N(R^5)SO_2N(R^6)(R^7)$,

provided that when t is zero and each of L^3 and L^4 is a covalent bond then u is the integer 1 and R^4 is other than a hydrogen atom;

L^2 is a covalent bond or an atom or group -O-, -S-, -C(O)-, -C(S)-, -S(O)-, $-S(O)_2$, $-N(R^8)$- ~~[where R^8 is a hydrogen atom or an optionally substituted C_{1-6}alkyl group]~~ or $-C(R^8)(R^{8a})$- ~~[~~(where R^{8a} is an atom or group as defined for R^8 and may be the same or different)~~]~~;

Ar^2 is an optionally substituted aromatic or heteroaromatic group;

Alk is a chain

$-CH_2CH(R)-$, $-CH=C(R)-$, $-\underset{\displaystyle CH_2R}{\overset{|}{CH}}-$ or $-\underset{\displaystyle CHR}{\overset{\|}{C}}-$

in which R is a carboxylic acid ($-CO_2H$) ~~or a derivative or biostere thereof~~, a carboxylic acid ester, a carboxylic acid amide, or a carboxylic acid biostere;

R^1 is a hydrogen atom or a C_{1-6}alkyl group;

L^1 is a covalent bond or a linker atom or group -O-, -S-, -C(O)-, -C(O)O-, -OC(O)-, -C(S)-, -S(O)-, $-S(O)_2$-, $-N(R^8)$-, $-N(R^8)O$-, $-N(R^8)N$-, $-CON(R^8)$-, $-OC(O)N(R^8)$-, $-CSN(R^8)$-,

-$N(R^8)CO$-, -$N(R^8)C(O)O$-, -$N(R^8)CS$-, -$S(O)_2N(R^8)$-, -$N(R^8)S(O)_2$-, -$N(R^8)CON(R^8)$-, -$N(R^8)CSN(R^8)$-, or -$N(R^8)SO_2N(R^8)$-;

Alk^1 is an optionally substituted aliphatic chain;

n is zero or the integer 1;

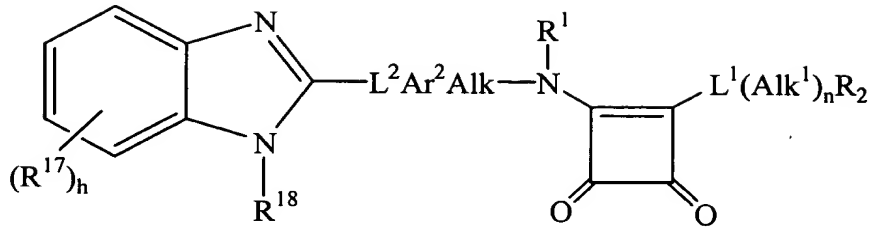
R^2 is a hydrogen atom or an optionally substituted heteroaliphatic, ~~cycloaliphatic,~~ C_{3-10}cycloalkyl, C_{3-10}cycloalkenyl, ~~heterocycloaliphatic,~~ C_{3-10}heterocycloalkyl, C_{3-10}heterocycloalkenyl, ~~polycycloaliphatic,~~ C_{7-10}bicycloalkyl, C_{7-10}tricycloalkyl, C_{7-10}bicycloalkenyl, C_{7-10}tricycloalkenyl, ~~heteropolycyclo-aliphatic,~~ C_{7-10}bicycloheteroalkyl, C_{7-10}tricycloheteroalkyl, C_{7-10}bicycloheteroalkenyl, C_{7-10}tricycloheteroalkenyl, aromatic or heteroaromatic group, wherein said heteroaliphatic, heterocycloalkyl, heterocycloalkenyl, bicycloheteroalkyl, tricycloheteroalkyl, bicycloheteroalkenyl and tricycloheteroalkenyl groups contain one, two, three, or four heteroatoms or heteroatom-containing groups as defined for L^3 and L^4, which may be the same or different;

provided that Het is not a 2,6-naphthyridin-1-yl, isoquinolin-1-yl, 2,7-naphthyridin-1-yl or quinazolin-4-yl group;

and the salts, solvates, hydrates and N-oxides thereof.

12. (Amended) A compound according to Claim 1 in which L^1 is a covalent bond, n is zero and R^2 is an optionally substituted ~~C_{5-7}heterocycloaliphatic~~ C_{5-7}heterocycloalkyl or C_{5-7}heterocycloalkenyl group.

15. (Amended) A compound according to Claim 1 of formula (2a):



(2a)

wherein:

R^{17} is an atom or group R^{16} as previously defined;

~~g is the integer 1, 2, 3 or 4;~~

h is zero or the integer 1, 2 or 3;

R^{18} is a hydrogen atom or an atom or group R^{16} as previously defined;

and the salts, solvates, hydrates and N-oxides thereof.

19., (Amended) A compound which is:

S-2-{[2-Dipropylamino)-3,4-dioxo-1-cyclobutenyl]amino}-3-{4-[(1-methylbenzimidazol-2-yl)amino]phenyl}propanoic acid;

S-2-{[2-Dipropylamino)-3,4-dioxo-1-cyclobutenyl]amino}-3-{4-[(1-methylbenzimidazol-2-yl)amino]phenyl}propanoic acid;

S-2-{[2-(2-Methylpiperidin-1-yl)-3,4-dioxo-1-cyclobutenyl]amino}-3-{4-[(1-methylbenzimidazol-2-yl)amino]phenyl}propanoic acid;

(*S*)-3-[4-(Thiophen[2,3-d]pyrimidin-4-ylamino)phenyl]2-(2-(diethylamino-3, 4-dioxocyclobut-1-enylamino)propanoic acid;

and the salts, solvates, hydrates, N-oxides and carboxylic acid esters~~, particularly the methyl, ethyl, propyl and i-propyl esters~~ thereof.

21. (Amended) A ~~compound~~ method for the ~~prophylaxis or~~ treatment of ~~a disease or disorder in a mammal in which the extravasation of leukocytes plays a role,~~ inflammatory arthritis, multiple sclerosis, allograft rejection, diabetes, inflammatory dermatoses, asthma or inflammatory bowel disease comprising administering to a mammal suffering from such a disease or disorder a therapeutically effective amount of a compound according to Claim 1.

23. (Amended) A method according to Claim ~~22~~ 21 wherein said inflammatory arthritis is selected from the group consisting of rheumatoid arthritis, vasculitis and polydermatomyositis.

24. (Amended) A method according to Claim ~~22~~ 21 wherein said inflammatory dermatoses are selected from the group consisting of ~~prosiasis~~ psoriasis and dermatitis.

25. (Amended) A method of inhibiting, in a mammal suffering from a disease or disorder associated with elevated α_4 integrin activity, the binding of $\alpha 4$ integrins to the ligands thereof, comprising administering to the mammal an effecting amount of a compound according to Claim 1.

26. (Amended) A method according to Claim 25 wherein the $\alpha 4$ integrins are selected from the group consisting of ~~$\alpha 4\beta 1$~~ $\alpha_4\beta_1$ and ~~$\alpha 4\beta 7$~~ $\alpha_4\beta_7$ integrins.

Claim 22 has been cancelled.

New claim 27 has been added.

APPENDIX A

GRANT & HACKH'S

CHEMICAL DICTIONARY

[*American, International, European and British Usage*]

Containing the Words Generally Used in Chemistry, and Many of the Terms Used in the Related Sciences of Physics, Medicine, Engineering, Biology, Pharmacy, Astrophysics, Agriculture, Mineralogy, etc.

Based on Recent Scientific Literature

FIFTH EDITION
Completely Revised and Edited by

ROGER GRANT

M.A., D. de l'U., Ph.D., C. Chem., M.R.S.C. *Consultant*

CLAIRE GRANT

M.B., B.S., M.R.C.P.E. *Medical Practitioner*

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The editors for this book were Betty J. Sun and Susan Thomas, the designer was Naomi Auerbach, and the production supervisor was Teresa F. Leaden. It was set in Palatino by University Graphics, Inc.

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Iodine cyanide. Colorless needles, soluble in water. **c. sulfide** $(CN)_2S$ = 84.1. Colorless scales, m.60, soluble in water.

cyanogenetic Yielding cyanogen; as, certain glucosides, amygdalin. Cf. *syncyanin.*

cyanohematin A compound of hematin and cyanogen.

cyanohydride Cyanohydrin.

cyanohydrin Cyanalcohol. A compound containing the radicals −CN and −OH. **c. synthesis** Addition of a carbon atom by the reaction $R{\cdot}HC{:}O + HCN \rightarrow R{\cdot}CHOH{\cdot}CN$. Cf. *Wohl's reaction.*

cyanol Aniline*.

cyanomaclurin (1) $C_{15}H_{12}O_6$ = 288.3. A tannin from the wood of *Arctocarpus integrifolia.* Colorless crystals, m.290. (2) A synthetic anthocyanidin.

cyanomethine $C_6H_9N_3$ = 123.2. 4-Amino-2,6-dimethylpyrimidine, cyamethine. Colorless crystals, m.180.

Cyanophyceae A group of blue algae. See *phycocyanin.*

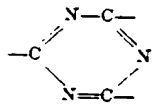
cyanosis A bluish-purple color of the skin and tongue, due to lack of oxygen in the blood.

cyanotype Blueprint.

cyanoximide A compound containing the radical $NC{\cdot}C(:NOH)-$.

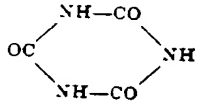
cyanoximidoacetic acid $NC{\cdot}C(:NOH){\cdot}COOH$ = 114.1. Colorless crystals, m.129. **c. acetic ester.** $NC{\cdot}C(:NOH)COOEt$ = 142.1. Colorless crystals, m.127.

cyanur Indicating the trivalent cyanidine ring



c.amine Melamine. **c.diamine** $C_3H_5ON_5$ = 127.1. Ammeline. Colorless crystals, decomp. by heat, insoluble in water. **c.monoamine** $C_3H_4O_2N_4$ = 128.2. Ammelide. Colorless crystals, insoluble in water. **c.triamine** Melamine.

cyanuric acid $HO{\cdot}C{:}(N{\cdot}C{\cdot}OH)_2{:}N{\cdot}2H_2O$ = 165.1. Pyrolithic acid, trihydroxycyanidine, pyrouric acid, pyruric acid. Colorless monoclinics, sparingly soluble in water. Cf. *cyanur, melem.* **iso ~** Tricarbimide. The ketone form of cyanuric acid and main tautomer.



thio ~ See *thiocyanuric acid.*

cyanuric azide $C_3N_3(N_3)_3$ = 204.11. Colorless crystals, m.94, insoluble in water; a detonating explosive.

cyanuric ester A derivative of cyanuric acid containing the radical $C_3N_3O_3$≡. **ethyl ~** $C_3N_3(OEt)_3$ = 213.2. Colorless crystals, m.29, b.275. **ethyliso ~** $C_3O_3N_3Et_3$ = 213.2. Ethyl tricarbimide. Colorless crystals, m.96. **iso ~** A derivative of isocyanuric acid, containing the isocyanur radical, $C_3H_3O_3N_3$≡. **methyl ~** $C_3N_3(OMe)_3$ = 171.2. Colorless crystals, m.135, soluble in alcohol. **methyliso ~** $C_3O_3N_3Me_3$ = 171.2. Methyl tricarbimide. Colorless crystals, m.175.

cyanuric trichloride Tricyanogen chloride.

cyanurin A blue compound produced in urine containing indican, on addition of an acid.

cybernetics The study of control and communications interrelationships among humans, machines, and social organization. Cf. *biomechanics.*

cybotactates Aggregates of molecules in liquids; generally oriented. Cf. *zone.*

cybotactic Pertaining to end-to-end or side-to-side arrangements of molecules. Cf. *bond, association.*

cybotaxis The cubic space arrangement of the molecules of noncrystalline substances.

cyclamates (1) Salts of cyclamic acid. (2) Sweeteners, as calcium c., about 30 times sweeter than sucrose; banned in the USA as possible carcinogens.

cyclamic acid $C_6H_{11}{\cdot}NH{\cdot}SO_3H$ = 179.2. Cyclohexylsulfamic acid. White, sweet crystals, m.179, soluble in water; a sweetening agent (BP).

cyclamin Arthranitin.

cyclamiretin $C_{15}H_{22}O_2$ = 234.3. A decomposition product of arthranitin.

cycle (1) Varve. Any periodic repetition of a phenomenon; nitrogen cycle. (2) A ring or closed atomic chain; as, homocycle. **megacycles per second** 1 Mc/s = 1 megahertz. —See *hertz.*

cyclic Arranged in a ring. Cf. *acyclic, aromatic.* **carbo ~** Indicating a ring of carbon atoms, e.g., benzene. **di ~** An atomic structure containing 2 rings, e.g., naphthalene. **hetero ~** A ring composed of 2 or more different kinds of atoms, e.g., pyridine. **hexa ~** An atomic structure containing 6 rings. **homo ~** A ring composed of one kind of atom. **mono ~** A molecule containing one ring only. **penta ~** An atomic structure containing 5 rings, e.g., morphine. **poly ~** An atomic structure containing 2 or more rings. **tetra ~** An atomic structure containing 4 rings. **tri ~** An atomic structure containing 3 rings.

c. action See *catalysis.* **c. compound** A compound that contains a ring of atoms, or a closed homocyclic or heterocyclic chain of atoms in its molecule. See *ring.* **c. hydrocarbons** Compounds of hydrogen and carbon, which contain a ring of carbon atoms. Cf. *benzene series, cycloparaffin.*

cyclite Benzyl bromide*.

cyclitols* Cycloalkanes with one OH group on each of 3 or more ring atoms; as, hexoses.

cyclization Ring formation.

cyclizine hydrochloride $C_{18}H_{22}N_2{\cdot}HCl$ = 302.8. Mar(e)zine. White, bitter crystals, m.285 (decomp.), soluble in water; an antihistamine and anti-travel-sickness remedy (USP, BP).

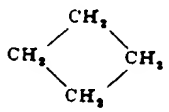
cyclo-* Prefix indicating a ring structure. It is italicized in inorganic names, but not in organic names.

cycloalkanes Generic name for saturated, monocyclic hydrocarbons, as, cyclohexane.

cycloalkyl Generic name for radicals derived from cycloalkanes; as, cyclohexyl.

cyclobarbitone $C_{12}H_{16}O_3N_2$ = 236.3. Phanodorm. White, odorless, slightly bitter crystals, m.172, slightly soluble in water; a sedative, used as c. calcium (EP, BP). See *barbiturates.*

cyclobutane* C_4H_8 = 56.1. *Tetramethylene,* q.v.



Citrus aurantium. Yellow powder, decomp. 251, soluble in water. It splits on hydrolysis to hesperitinic acid, glucose, and phloroglucinol.

hesperidine An alkaloid from the leaves of *Peucedanum galbanum*, wild celery (Umbelliferae).

hesperitinic acid $C_{10}H_{10}O_4$ = 194.2. 3-Hydroxy-4-methoxycinnamic acid, isoferulic acid. Yellow needles, m.233.

Hess H., **Germain Henri (1802–1850)** German-born Russian chemist, and a founder (1840) of thermochemistry. **H., Victor Franz (1883–1964)** German physicist, noted for work on cosmic radiation. Nobel prize winner (1936). **H. law** The law of constant heat summation. The net amount of heat liberated or absorbed in a chemical reaction is the same, whether the reaction is performed in one or successive steps. **H. rays** Cosmic rays. **H. viscosimeter** A graduated capillary tube with a rubber bulb, used for determining the viscosity of biological solutions.

hessian A plain woven fabric of hemp or jute. Used for sacking, and as waste for paper manufacture. C. *botany*. **h. crucible** (1) A sand crucible. (2) A large clay crucible.

hessite Ag_2Te. Silver telluride. A black mineral, d.8.3–9, hardness 2.5–3.

hessonite $Al_2(Ca,Fe)_2Si_3O_{16}$. Cinnamon stone. A garnet, d.3.5, hardness 6.5–7.

Het Acid Trademark for 1,4,5,6,7,7-hexachlorobicyclo(2.2.1]-5-heptene-2,3-dicarboxylic acid. Unique among dibasic acids in containing over 54% by weight of stable Cl. Used to impart flame resistance to resins.

hetero- Prefix (Greek) indicating "unlikeness" or "difference."

heteroalbumose A form of albumose, insoluble in water, precipitated by saturation with sodium chloride.

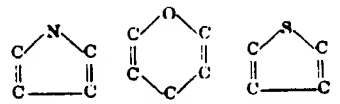
heteroartose The protein $C_{74}H_{130}N_{20}O_{24}S$.

hetero atom* A heterocyclic atom.

heterobaric Possessing different mass numbers; as, isotopes.

heterocycle A ring of different types of atoms. Antonym: homocycle. See *heterocyclic compound*.

heterocyclic* Pertaining to dissimilar atoms in a ring. **h. atom** Any atom, other than carbon, C, in an atomic ring; e.g., N, O, S, Se, P, As. **h. compound** A ring compound having atoms other than C in its nucleus; as:



Antonym: homocyclic.

heterofil A composite filament, in which polymers of different characteristics are spun together so that the filaments coalesce longitudinally.

heterogeneity The state of being composed of particles or aggregates of different substances; hence, matter that is of dissimilar composition. Antonym: homogeneity.

heterogeneous Opposite to *homogeneous*, q.v. *(homogeneity)*. Describes a substance that consists of more than one phase, and therefore is not uniform; as, colloids. **h. reaction** A chemical change in which 2 or more reactions take place simultaneously.

heterogenesis The derivation of a living thing from something unlike itself; e.g., of viruses from the complex cell.

hetero ion An adsorption complex ion whose charge is due to an adsorbed simple ion, e.g., a protein complex with adsorbed OH^-.

heterolysis (1) The dissolution of a cell by an external agent. Cf. *autolysis*. (2) The hemolytic action of the blood serum of one animal species on the blood cells of another species. (3) A reaction in which a bond is severed and one fragment retains both bonding electrons: A: B→A + : B. Cf. *homolysis*.

heterolyzate The filtered liquid portion of the products of heterolysis.

heterometry A form of turbidimetric titration in which nucleating chemical systems are studied by light absorption measurements.

heterophase Forming 2 or more states of aggregation. Cf. *phase*.

heteropolar An unequal distribution of electric charges in a bond, so that one atom is more positive or negative than the other. Cf. *homopolar*.

heteropoly acids The complex acids of heavy metals with phosphoric acids; as, phosphomolybdic acid.

heteropoly blue Molybdenum blue.

heterotopes Elements having different atomic numbers and, therefore, occurring in different parts of the periodic table. Antonym: isotopes. Cf. *isobar*.

heterotype A compound which differs in properties from compounds of a similar type.

hetol Sodium cinnamate.

hetralin $C_6H_{12}N_4 \cdot C_6H_4O_2$ = 278.3. Dihydroxybenzenehexamethylenetetramine. Colorless needles, decomp. 155, soluble in water; a substitute for hexamethylenetetramine.

heulandite $CaAl_2Si_6O_{15}$. A zeolite.

heuristic Describing an approach to scientific problems involving trial-and-error procedures.

Heusler alloys See *Heusler's alloy* under *alloy*.

Hevea See *rubber*.

Hevesy, George de (von) (1885–1966) Hungarian-born German chemist, codiscoverer of hafnium. Nobel prize winner (1943).

hex Hexamethylenetetramine.

hexa- Prefix (Greek) denoting "six."

hexaammine* Indicating 6 $-NH_3$ groups. **h.cobalt (III)*** The cation $[Co(NH_3)_6]^{3+}$.

hexaaqua* Indicating 6 H_2O molecules. **h.chromium (III)*** The cation $[Cr(H_2O)_6]^{3+}$.

Hexa-Betalin Trademark for pyridoxine hydrochloride.

hexabiose Hexobiose. A carbohydrate (disaccharide) consisting of 2 hexoses; as, lactose, sucrose.

hexaborane* B_6H_{10} = 74.9. Colorless liquid, m. −65, decomp. in water.

hexabromide number An analytical value of fats indicating their content of acids with 3 (or more) double bonds; the mg of Br needed to brominate 100 g fat.

hexabromo-* Prefix indicating 6 Br atoms. **h.ethane** C_2Br_6 = 403.4. Yellow needles, decomp. 210, slightly soluble in water. **h.silicoethane** See *silicon bromides*.

hexachloro-* Prefix indicating 6 Cl atoms. **h.benzene** C_6Cl_6 = 284.8. Colorless needles, m.229, insoluble in water. Used in organic synthesis, in airfield flares, and in waterproofing of dopes. Cf. *benzene* hexachloride. **h.ethane** C_2Cl_6 = 236.7. Carbontrichloride, hexoram. White, rhombic crystals, m.184, insoluble in water. Has an inherent tendency to agglomerate; so additives used to improve flow and stability. Used in organic synthesis; the manufacture of explosives and fireworks, smoke screens, and disinfectants. Cf. *H.C.* **h.platinate(IV)*** Chloroplatinate. A salt of h. platinic acid, containing the anion $[PtCl_6]^{2-}$. **h.platinic acid*** See *hexachloroplatinic acid* under *platinic acid*.

hexachlorophane BP name for hexachlorophene.

hexachlorophene $C_{13}H_4O_2Cl_6$ = 406.93. 2,2'-Methylenebis(3,4,6-trichlorophenol). Hexachlorophane. Phisoscrub, Sterzac. White crystals with phenolic odor,

styrolene, phenethylene, styrol, vinylbenzene, cinnamene, phenylethylene. A constituent of storax, essential oils, and coal tar. Colorless, aromatic liquid, d.0.925, b.145, soluble in alcohol. Used in organic synthesis, and forms 2 types of derivatives; as *o-*, *m-*, and *p*-aminovinylbenzene = $NH_2C_6H_4CH{:}CH_2$. *p*-phenylvinylamine = $C_6H_5CH{:}CHNH_2$. (2) The radical $-CHPh\cdot CH_2-$.

styrilic acid Cinnamyl alcohol.

Styroflex Trademark for a polystyrene synthetic fiber.

styrol (1) Styrene*. (2) Colloidal silver.

styrolene Styrene*. **s. alcohol** Cinnamyl alcohol*.

Styron Trademark for polymerized styrene.

styrone Cinnamyl alcohol*.

styryl* 2-Phenylethenyl†. Cinnamenyl. The radical $PhCH{:}CH-$, from styrene. **s. alcohol** Cinnamyl alcohol*. **s.amine*** $PhCH{:}CH\cdot NH_2$ = 119.2. Colorless liquid, b.236, insoluble in water. **s. ketone** $(PhCH{:}CH)_2CO$ = 234.3. Dibenzylideneacetone. 1,5-Diphenyl-1,4-pentadien-3-one*. Colorless crystals, m.112. **3-s.-2-propenoic acid*** $C_6H_7CH{:}CH\cdot COOH$ = 174.2. Colorless crystals, m.165.

S.U. Strontium unit.

sub- Prefix (Latin), indicating "below," "almost," "under," or "near." Formerly designating a lower form of oxidation or a basic compound, and a deficiency of the substance or radical it described. Cf. *per-*.

subacetate A basic acetate; as, lead subacetate.

subatomic Pertaining to the structure of actual atoms as distinct from their function as parts of a molecule. **s. decomposition** Radioactive disintegration. **s. particle** See *subatomic particle* under *particle*. **s. reaction** A change in which an atom is disintegrated or transformed. See *nuclear chemistry*.

subatomics The study of the structure of atoms and the role of electrons and nuclei in subatomic changes.

subcarbonate A basic carbonate.

subcutaneous Located beneath the skin. **s. injection** The administration of a drug by injection under the skin.

suber Cork.

suberane Cycloheptane*.

suberic acid $(CH_2)_6\cdot(COOH)_2$ = 174.2. Octanedioic acid*, 1,6-hexanedicarboxylic acid*. A homolog of oxalic acid, obtained by oxidation of cork. Colorless needles, m.140, soluble in water.

suberin A polysaccharide constituent of wood bark.

suberol Cycloheptanol*.

suberone Cycloheptanone*.

suberyl The cycloheptyl* radical. **s. alcohol** Cycloheptanol*.

subhalide A compound of the type $X_2M\cdot MX_2$; e.g., B_2Cl_4.

sublamine $HgSO_4\cdot 2C_2H_4(NH_2)_2\cdot 2H_2O$ = 424.8. Mercuric sulfate ethylenediamine. White crystals, soluble in water.

sublation A flotation process in which material absorbed on the surface of gas bubbles is collected on a layer of immiscible liquid, instead of as a foam over a liquid aqueous phase.

sublethal Not quite fatal. **s. dose** A quantity of drug below the fatal dose.

sublimate (1) The deposit formed on heating substances which pass directly from the solid to the vapor phase and then back to the solid state. Cf. *distillate*. (2) Mercuric chloride. **corrosive ~** Mercuric chloride.

sublimation The production of a sublimate; used to purify substances; as, iodine.

Sublimaze Trademark for fentanyl citrate.

submicron See *micron*.

subnitrate A basic nitrate, as, bismuth subnitrate.

subnormal Below normal.

suboxide That oxide of an element which contains the lowest proportion of oxygen.

subshell. See *shell (4)*.

subsoil The layer below the surface soil. It contains the rain-soluble organic portion of the soil.

subsonic Describing a velocity less than that of sound.

substance The material of which a body is composed; as a chemical compound. **s. concentration** See *concentration*.

substantive dyeing The coloring of fabrics with dyestuffs, without mordants.

substantive dyes A group of coal tar colors, chiefly for cotton, that dye without mordants; as benzidine dyes.

substituent* Any atom or group replacing the hydrogen of a parent compound.

substitute To replace one element or radical in a compound by a substituent.

substituted Pertaining to a compound which has undergone substitution. **s. compound** A compound obtained by substitution; a *derivative*, q.v.

substitution A reaction in which an atom or group of atoms in a (usually organic) molecule is exchanged for another. **cine ~** Reaction in which the entering group occupies the position next to that of the group being substituted.

substitutive nomenclature See *nomenclature*.

substrate The material upon which an enzyme acts.

substructure searching Computerized approach to searching a data base of chemical information for substances that contain particular combinations and arrangements of atoms and bonds.

subsubmicron Amicron.

subsulfate A basic sulfate.

subtilin An antibiotic polypeptide produced by *Bacillus subtilis*, especially from the fermentation of asparagus canning waste.

subtilisin* A proteolytic enzyme that degrades tissue proteins. Used to isolate drugs from tissues before analysis.

subtractive nomenclature See *nomenclature*.

subultramicroscopic Invisible in the ultramicroscope. Cf. *amicron*.

Sucaryl Trademark for sodium cyclohexylsulfamate, a nonsugar sweetening agent.

succinaldehyde* $C_2H_4(CHO)_2$ = 86.1. Butanedial*, b.170 (decomp.). **polymeric ~** m.65.

succinamic acid* $H_2N\cdot C(O)\cdot CH_2\cdot CH_2\cdot COOH$ = 117.1. 3-Carbamoylpropionic acid*. Amidosuccinic acid. White powder, soluble in water. **amino ~** Asparagine*.

succinamide* $(NH_2COCH_2)_2$ = 116.1. Butanediamide*. Colorless needles, m.242 (decomp.), soluble in water. **hydroxy ~** Malamide*.

succinamoyl The radical $-OC(CH_2)_2CONH_2$.

succinamyl The succinamoyl* radical.

succinate* $C_2H_4(COOM)_2$. A salt of succinic acid.

succinelite Succinic acid from amber.

succinic **s. acid*** $HOOC\cdot CH_2\cdot CH_2\cdot COOH$ = 118.1. Butanedioic acid*, ethylenedicarboxylic acid, amber acid. Occurs in amber and other resins as colorless, monoclinic prisms, m.184, slightly soluble in water; a reagent. **iso ~** $CH_3\cdot CH(COOH)_2$. A solid, m.130 (decomp.), soluble in alcohol. **2-amino ~** Aspartic acid*. **diamido ~** Succinamide*. **dihydroxy ~** Tartaric acid*. **ethyl ~** See *ethylsuccinic acid* under *ethyl*. **formyl ~** Aconic acid. **hydroxy ~** Malic acid*. **mercapto ~*** Thiomalic acid. **methyl ~** Pyrotartaric acid. **methylene ~** Itaconic acid. **oxo ~** Oxalacetic acid*.

APPENDIX B

GRANT & HACKH'S

CHEMICAL DICTIONARY

[*American, International, European and British Usage*]

Containing the Words Generally Used in Chemistry, and Many of the Terms Used in the Related Sciences of Physics, Medicine, Engineering, Biology, Pharmacy, Astrophysics, Agriculture, Mineralogy, etc.

Based on Recent Scientific Literature

FIFTH EDITION
Completely Revised and Edited by

ROGER GRANT

M.A., D. de l'U., Ph.D., C. Chem., M.R.S.C. *Consultant*

CLAIRE GRANT

M.B., B.S., M.R.C.P.E. *Medical Practitioner*

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solution. **physical ~** A s. in which solute and solvent mix but do not react chemically; the solute can be recovered on evaporation, the solvent by distillation. Cf. *chemical solution.* **physiological ~** Isotonic s. **saturated ~** A s. that normally contains the maximum amount of substance able to be dissolved. **solid ~** See *solid solution, sosoloid.* **standard ~** A s. that contains a definite amount of substance dissolved; as, a molar s. **standardized ~** A s. adjusted to a known concentration. **supersaturated ~** A s. that contains a greater quantity of solid than can normally be dissolved at a given temperature; on slow cooling, the excess precipitates under suitable conditions. **test ~** T.S. A reagent s. **volumetric ~** V.S. A standard analytical s., usually containing 1, $\frac{1}{2}$, or $\frac{1}{10}$ mole of a substance dissolved in 1 liter of water.

s. mining Winning soluble salts (as potassium chloride) by pumping water into the formation and evaporating the resulting solution. E.g., Frasch process. **s. pressure** The tendency of atoms or molecules to mix with a liquid, or to dissolve in it; measured by the osmotic pressure. **s. tension** The tendency of atoms or molecules to dissolve in a liquid and form ions; measured by the electromotive force. See *Nernst theory.* **s. theory** See *Nernst theory, Arrhenius theory.*

solvate A molecular or ionic complex of molecules or ions of solvent with those of solute; as $Cl(H_2O)_n^-$. The ions are surrounded by a zone of oriented water molecules. **crystalline ~** A crystal containing solvent as part of its lattice. **s. theory** The abnormalities of solutions are due to the formation of complexes between the ions or molecules of the solute and solvent. Cf. *hydration.*

solvation Any stabilizing interaction between solute and solvent; if the latter is water, hydrates or hydrated ions are formed, e.g., $M(H_2O)_n$.

solvatochromism The formation, by molecular addition, of a colored complex (solvate) between colorless molecules of organic compounds and those of other compounds.

Solvay S., Ernst (1838–1922) Belgian industrial chemist. **S. process** Making sodium carbonate and calcium chloride by treating sodium chloride with ammonia and carbon dioxide. The sodium hydrogencarbonate produced is heated and some carbon dioxide recovered; the ammonia is recovered by lime or magnesia.

solvent (1) That component of a homogeneous mixture which is excess. (2) A liquid which dissolves another substance (solute), generally a solid, without any change in chemical composition; as, water containing sugar. (3) A liquid that dissolves a substance by chemical reaction; as, acids and metals. [illegible] that acts as an acid by losing a proton [illegible] Water. **associating ~** A s. [illegible] forms complexes; as, water. Cf. *bond.* **basic ~** [illegible] as a base by gaining a proton from the [illegible] See (3). **ionizing ~** See *polar solvent.* [illegible] Organic liquids used to dissolve resins and [illegible] **low-boiling ~** b. below 100 (alcohol). [illegible] **~** b. near 125 (toluene). **high-boiling ~** [illegible] (xylene). **plasticizer and softener ~** b. near 300 [illegible] Flux. **nonaqueous ~** A solvent [illegible] water. **nonassociating ~** A s. that does not form [illegible] between its molecules or ions and the solute; as, benzene. **nonionizing ~** Nonpolar. **nonpolar ~** A s. that does not conduct an electric current; as, hydrocarbons. **normal ~** Nonassociating. **physical ~** A s. that does not react chemically with the solute. **polar ~** A s. that produces electrically conducting solutions (as, water), and causes dissociation of the solute into ions. **two-type ~** A s. having 2 groups which confer s. properties; as alcohol-ethers, $HO \cdot R \cdot O \cdot R$; e.g., Cellosolve. **universal ~** Aqua regia.

s. action A process of making substances water-soluble.

solvolysis The effect of the nucleophilic character of a solvent on the reactions of the solute dissolved in it.

solvolytic Pertaining to solvation. **s. dissociation** Ion formation in a nonaqueous solution. Cf. *solvate theory.*

somatic Pertaining to the body; usually to cells other than gametogenic and gemete cells. S. cells have the diploid number of chromosomes.

sombrerite A "hard" mineral phosphate (35% phosphorus pentaoxide); a source of phosphorus.

Sommelet reaction The production of benzaldehyde by reaction between benzylamine and formaldehyde, preferably in presence of hexamine.

Sommerfeld S., Arnold (1868–1951) German physicist; developed quantum theory of atomic structure. **S. notation** See *quantum number.*

somnifacient A *hypnotic,* q.v.

somnirol $C_{32}H_{44}O_7$ = 540.7. A monohydric alcohol of *Withania* species (Solanaceae).

Somnitol $C_{33}H_{44}O_7$ = 554.7. Trademark for an alcohol from *Withania* species (Solanaceae).

Somophyllin Trademark for aminophylline.

Soneryl Trademark for butobarbital.

sonic Phonic. Pertaining to sound which is audible to the human ear. See *sound frequency.* Cf. *infrasonic, ultrasonic.*

Sonnenschein S., Franz Leopold (1819–1879) German forensic analyst. **S.'s reagent** A solution of phosphomolybdic acid forms a yellow precipitate with the sulfates of alkaloids.

sonochemistry The use of high-intensity ultrasound radiation to induce chemical reactions. Acoustic cavitation causes localized areas of high temperature and pressure.

sonoluminescence Luminescence induced by sound waves.

sonometer Phonometer. An instrument to measure sound vibrations.

sonora gum The exudiations of the creosote bush, *Covillea tridentata* (Mexico.).

soot An impure black carbon containing oily and empyreumatic compounds from the incomplete combustion of resinous materials or wood. It contains hydrocarbons, and if derived from coal, ammonium sulfate. Cf. *lampblack.*

sophora Coral bean. The poisonous seeds of *Sophora speciosa* (Leguminosae), India.

sophorine An alkaloid from *Sophora* species. Colorless liquid resembling cystine and matrine. Cf. *kuhseng.*

soporific An agent that produces sleep. Cf. *hypnotic.*

sorbic acid (*E,E*)-2,4-Hexadienoic acid*. **hydro ~** Hexenoic acid*. **para ~** A lactonelike compound forming sorbic acid when heated with acid or alkali.

sorbide Sorbitan with one further water molecule removed. Any of a group of surfactants, used as emulsifiers.

sorbin, sorbinose Sorbose.

sorbitan $C_6H_8O(OH)_4$ = 164.1. Sorbitol anhydride. Generic name for anhydrides of sorbitol; derived by removal of 1 molecule of water. With fatty acids, as oleic and stearic, sorbitans form nonionic surface-active agents that are used as emulsifiers. Cf. *sorbide.*

sorbite (1) Sorbitol. (2) A mixture of ferrite and cementite, with conglomerations of carbon in steel; a transition form between pearlite and troostite.

sorbitol $HO \cdot H_2C(CHOH)_4CH_2OH$ = 182.2. Glucitol†, sorbite. **D- ~** Occurs in many plants. Colorless crystals, m.111, soluble in water. Used chiefly for the preparation of

APPENDIX D

natalizumab

Standard | Summary

Last Updated	February 2002
Highest Dev. Status	Phase II Clinical
Indication	Inflammatory bowel disease, Multiple sclerosis, Ulcerative colitis, Crohn's disease
Action	Integrin modulator, Cell adhesion molecule inhibitor
Technology	Monoclonal antibody, Humanized
Company	Elan Pharmaceuticals Inc

Summary

Natalizumab, a humanized monoclonal antibody specific for the alpha-4 beta-1 integrin (VLA4) expressed on leukocytes, is being developed by Elan (formerly Athena Neurosciences) and Biogen as a potential treatment for chronic multiple sclerosis (MS), inflammatory bowel disease (IBD), Crohn's disease (CD) and ulcerative colitis (UC). Several phase II trials have been completed [**313095**], [**275424**]. By May 2001, all phase II trials were completed [**412878**], [**413862**]. In July 2001, analysts expected that the earliest launch date would be in the second half of 2004 [**416802**]. Phase III trials for the treatment of MS began in December 2001 [**434121**]. In January 2002, it was reported that natalizumab had also entered phase III trials for CD [**436146**].

Multiple Sclerosis

In December 2001, Elan and Biogen had enrolled and dosed the first patients in their multicenter phase III clinical trials of Antegren (natalizumab) in MS. Elan and Biogen expected to enroll and dose the first patients in their phase III clinical trials for Crohn's disease before the end of 2001 [**434121**].

The first of the studies conducted was a phase II, double-blind, placebo-controlled trial which involved 213 MS patients at 26 sites in the US, Canada and the UK. Patients (suffering from either relapsing-remitting MS or secondary progressive MS) received monthly doses of natalizumab or placebo over a 6-month period. The primary endpoint, of a reduction in new gadolinium-enhancing lesions compared to placebo over the 6-month treatment period, was achieved with a high degree of statistical significance [**396629**]. The full phase II study data for multiple sclerosis were presented at the congress of the European Committee for the Treatment and Research in Multiple Sclerosis (ECTRIMS) in September 2001 in Dublin, Ireland. In the placebo group the mean of new gadolinium-enhancing lesions was 9.6, whereas that of the natalizumab-treated groups ranged from 0.6 to 1.2 according to dose group. Treatment was generally well tolerated. Adverse effects included headache, asthenia and urinary tract infections and infrequent hypersensitivity-like reactions. Based on the above data, the companies aim to commence two phase III MS studies, studying natalizumab as a monotherapy as well as in combination with Biogen`s interferon beta-1a (qv) [**416802**], [**422339**].

In a double-blind, placebo-controlled, phase II study conducted at eight centers in the UK, 70 patients with MS were assessed over a 12-week period. Natalizumab showed a significant reduction in new brain lesions as measured by MRI, compared to placebo [**275424**]. Further phase II MS results were reported in July 1999. The trial investigated natalizumab in the treatment of acute exacerbation in patients with MS. The results were consistent with results observed in a previous multiple-dose phase II study indicating the potential utility of natalizumab for chronic treatment of patients with MS, but the results do not support further development for the treatment of acute exacerbation; that program has therefore been discontinued [**333924**].

Crohn's Disease

In May 2001, results of a phase II trial were presented at Digestive Disease Week in Atlanta, GA. A European multicenter study (CD202), sponsored by Elan Pharmaceuticals and Biogen, enrolled 244 individuals with chronic active CD (CDAI score = 220 to 450). Patients received either (i) 6 mg/kg iv natalizumab at weeks 0 and 4; (ii) 3 mg/kg iv natalizumab at weeks 0 and 4; (iii) 3 mg/kg iv natalizumab at week 0 then placebo at week 4; or (iv) placebo at weeks 0 and 4. The primary endpoint was the number of patients in remission at week 6 (CDAI < 150). Many patients were taking concomitant steroids or immunosuppressives, and medication was continued throughout the trial. A significant clinical response (CDAR decrease > 70) to natalizumab was noted at week 2 and was sustained throughout the 12 weeks, with a maximal response of 74% observed in the 3 mg group, compared to 38% in placebo. Remis sion occurred in 46% of 3 mg group (27% in placebo). In addition, a significant improvement in quality of life, as assessed by questionnaire, was observed. There was no significant difference in adverse events between treatment groups and placebo. There were two incidences of infusion reaction, and one patient expressed antibodies to natalizumab. Further trials were planned with the 3+3 dose regimen at this time [**409094**], [**410251**], [**412689**], [**413891**]. A pivotal phase III trial was expected in the second half of 2001 [**422425**].

A separate phase II, double-blind, placebo-controlled study conducted across 38 sites in eight European countries included 240 patients with moderate to severe CD. Patients received doses of natalizumab or placebo at week 0 and week 4. This study also demonstrated statistically significant positive results on multiple endpoints, including induction of remission as measured by the CD activity index. Further information about the potential safety and efficacy of natalizumab were due to be presented at a scientific conference in 2001 [**396629**].

In two separate pilot studies involving a total of 40 patients suffering from CD or UC, a positive trend towards efficacy was noted and natalizumab treatment was well tolerated in all three studies. Interim analysis of phase II data show positive results [**179966**], [**276967**]. Results from a 30-patient CD trial were reported at DDW in May 1999. Natalizumab was shown to be safe and well tolerated at 3 mg/kg. There was a positive efficacy trend [**327248**]. Serum samples from patients treated with natalizumab showed reduced levels of soluble VCAM-1 and increased

numbers of circulating lymphocytes expressing ICAM-1 [366475], [368058].

Additional Information

The company conducted UK phase I trials between June and December 1995. These trials involved 35 healthy volunteers, with the aim of determining safety and pharmacokinetic data [179966]. The results showed that the product was well-tolerated and had an acceptable safety and pharmacokinetic profile [200972].

Athena (now Elan Pharmaceuticals) showed in preclinical experiments that by blocking this integrin, leukocyte migration into the brain is blocked. In the experimental allergic encephalomyelitis model of MS, treatment with the antibody resulted in the reversal of induced paralysis and a reduction in myelin destruction. Also, MRI demonstrated a reduced edema within the CNS and a decreased blood-brain barrier permeability to CNS imaging agents in treated animals [222522].

VLA4 specifically binds to VCAM-1, a ligand present on brain endothelial cells, which is a potential mediator of autoimmune disorders, leading to MS [222518].

One of the major drawbacks with the use of natalizumab has been its lack of oral bioavailability, and this large molecule was split up into smaller molecules which have shown promising activity in animal models of MS and IBD.

The humanized antibody, natalizumab, is claimed in the associated patent, WO-09519790. VLA-4 itself and monoclonal antibodies for the integrin were first described in a patent (EP-00330506) by the Dana-Farber Cancer Institute.

In April 1998, Protein Design Labs granted a worldwide, nonexclusive license for natalizumab under its antibody humanization patents, to a subsidiary of Elan [286198].

In April 2000, Merrill Lynch forecast that the drug would be launched in 2001 [364935]. In September 2000, Merrill Lynch expected NDA filing to take place in 2003, with a launch in 2004 if the on-going development program remains on track [382577]. In August 2000, Merrill Lynch predicted sales of natalizumab of $50 million in 2002, rising to $150 million in 2004 [383230]. In September 2000, analysts Merrill Lynch predicted a launch in 2004 with sales estimated at $50 million for the full year [383742]. In April 2001, ABN AMRO predicted launch in 2004 for MS and Crohn's disease with sales of $50 million [422425]. In September 2001, Salomon Smith Barney estimated sales of $20 million i n 2004 [422373].

Development Status

Developer	Country	Status	Indication	Date	Confidence	Reference
Axogen Ltd	UK	Phase 2 clinical	Multiple sclerosis	29-Oct-96	Not Evaluated	223736
Axogen Ltd	US	Phase 2 clinical	Multiple sclerosis	29-Oct-96	Not Evaluated	223736
Biogen Inc	UK	Phase 2 clinical	Multiple sclerosis	08-Aug-00	Not Evaluated	379455
Biogen Inc	UK	Phase 2 clinical	Ulcerative colitis	08-Aug-00	Not Evaluated	379455
Biogen Inc	UK	Phase 2 clinical	Inflammatory bowel disease	08-Aug-00	Not Evaluated	379455
Biogen Inc	UK	Phase 3 clinical	Crohns disease	16-Jan-02	Not Evaluated	436146
Biogen Inc	US	Phase 3 clinical	Multiple sclerosis	19-Dec-01	Not Evaluated	434121
Elan Corp plc	UK	Phase 2 clinical	Inflammatory bowel disease	27-Jul-99	Not Evaluated	333924
Elan Corp plc	UK	Phase 2 clinical	Ulcerative colitis	23-Jan-98	Not Evaluated	275424
Elan Corp plc	UK	Phase 3 clinical	Crohns disease	16-Jan-02	Not Evaluated	436146
Elan Corp plc	US	Phase 3 clinical	Multiple sclerosis	19-Dec-01	Not Evaluated	434121
Elan Pharmaceuticals Inc	UK	Phase 2 clinical	Multiple sclerosis	29-Oct-96	Not Evaluated	223736
Elan Pharmaceuticals Inc	US	Phase 2 clinical	Multiple sclerosis	27-Mar-96	Not Evaluated	203340
Protein Design Labs Inc	US	Discovery	Multiple sclerosis	08-May-98	Not Evaluated	286198

[illegible]	Type
[illegible]	INN
[illegible]	Research Code
[illegible] integrin MAb, Athena	[illegible]
Antegren	Trade Name
AN100226	Research Code
VLA-4 MAb, Athena	[illegible]
CAS	
[illegible]-10-7	Immunoglobulin G4, anti-(human integrin alpha 4) (human-mouse monoclonal AN100226 gamma 4-chain), disulfide with human-mouse monoclonal AN100226 light chain, dimer

[illegible]

Mariano Elices, Integra LifeSciences Corp, San Diego, CA, USA

[illegible]

[illegible]

Antegren is a humanized monoclonal antibody (mAb) against the integrin subunit alpha4 (CD49d). The integrin alpha4 can pair with either of two subunits to form a cell surface heterodimeric receptor, namely, alpha4/beta1 (very late antigen (VLA)-4, CD49d/CD29), or alpha4/beta7. VLA-4 is being vigorously pursued as a therapeutic target for chronic inflammatory diseases due to its relatively well known biology **[265753]**, **[265775]**, **[279211]**. Currently, Antegren, the most advanced agent in the clinic, is undergoing evaluation as a therapy for MS and inflammatory bowel diseases.

VLA-4 is an active participant in the inflammatory cascade **[279211]**, by virtue of its molecular interactions with alternatively spliced fibronectin-containing CS-1 (CS-1-fibronectin) **[279215]**, **[279211]**, **[285283]**, and vascular cell adhesion molecule (VCAM)-1 **[279228]**,**[265775]**,**[279233]**. Expression of both CS-1-fibronectin and VCAM-1 has been demonstrated in rheumatoid arthritis **[266400]**,**[279238]**. In addition, various immunohistopathological studies have shown the presence of either VCAM-1, or CS-1-fibronectin in chronic inflammatory lesions, including atherosclerosis **[279240]**,**[279245]**, arteriopathy **[265791]**, cardiac and kidney allografts **[265791]**,**[279249]**, and glomerulonephritis **[279250]**. Taken together, these data suggest that VLA-4 mediates selective leukocyte recruitment in chronic inflammatory disorders.

Among human peripheral blood cell populations, alpha4 integrins are expressed on T-lymphocytes and monocytes **[265759]**,**[265756]**, and also on eosinophils **[279252]**,**[101722]**, **[279258]**, **[279259]**, **[279261]**. In contrast, alpha4 is either absent, or expressed at very low levels, on platelets and neutrophils **[265759]**, **[265760]**, **[265763]**. Consequently, blockade of alpha4 integrins, eg, VLA-4, is expected to be efficacious in chronic diseases mediated by T-cell, monocyte, or eosinophil infiltration (eg, multiple sclerosis (MS) and asthma). In contrast, VLA-4 therapy is anticipated to have little or no impact in acute inflammation, and cause few general immunosuppressive side effects.

Synthesis and SAR

A multitude of anti-VLA-4 mAbs have been generated that are specific to mouse, rat and human alpha4 integrin antigens **[265753]**. In addition, some of these mAbs display immune cross-reactivity with guinea pig, rabbit, sheep, and primate alpha4 **[265753]**. In summary, the availability of anti-alpha4 mAbs to several animal species has helped elucidate in vivo pathophysiology of VLA-4 in preclinical pharmacology models.

Pharmacology

T-lymphocyte recruitment to the central nervous system (CNS) was one of the first in vivo functions for VLA-4 to be discovered **[279263]**, **[265840]**. In fact, using mouse encephalitogenic T-cell clones, Janeway and coworkers demonstrated that entry into brain parenchyma by CD4+ T-lymphocytes required high surface expression of alpha4 integrin **[265840]**. Furthermore, the severity of adoptively transferred experimental autoimmune encephalomyelitis (EAE, a rodent surrogate model of human MS), and the degree of perivascular T-cell infiltration caused by the former clones correlated with alpha4 expression **[265840]**. Consistent with the role of VLA-4 in EAE, a single administration with either anti-VLA-4, or anti-VCAM-1 at the time of EAE transfer resulted in retardation of clinical symptoms **[265840]**. This suggests the involvement of the VLA-4/VCAM-1 pathway in mononuclear leukocyte trafficking through the CNS.

The mouse counterpart of Antegren, MAb AN-100226m, has been tested in active, as opposed to passive or adoptively transferred, EAE in guinea pigs **[265842]**. Not only does treatment with AN-100226m, prior to development of active EAE, suppress the initiation of clinical symptoms, but disease reversal is also observed following AN-100226m administration, after onset of clinical signs **[265842]**. Moreover, AN-100226m therapy resulted in clearance of monocytes and T-lymphocytes from perivascular and parenchymal areas in the CNS, and demonstrated a neuroprotective effect against demyelination of the white matter **[265842]**. Similar data were obtained in a separate study from the same investigators using a different anti-alpha4 mAb, administered as late as three and a half weeks after disease onset **[279265]**. In conclusion, VLA-4 treatment shows efficacy in preclinical disease models of MS, even when therapy commences after neurological symptoms have already become apparent.

Clinical Development

Phase I
A double-blind dose-escalation study of Antegren was performed in patients with clinically diagnosed MS to evaluate

safety, tolerability, and pharmacokinetic (PK) profile [**344444**]. Antegren was administered as a single iv infusion at increasing concentrations. Three patients received doses of 0.03, 0.1 and 0.3 mg/kg, respectively while two groups of six patients received 1, and 3 mg/kg. As control, a total of seven additional patients, distributed among the five Antegren dosing groups, received placebo. The drug was safe and well tolerated at all doses tested. Symptoms following treatment were evaluated by recording vital signs, laboratory chemistry, hematology and urinalysis, and electrocardiogram (EKG). Adverse events were generally mild, and no differences were apparent among various dosing groups. Headache was the symptom most frequently reported, but it occurred almost equally in both placebo (86%), and drug (81%) groups. Pharmacokinetic parameters for the 3 mg/kg iv drug infusion showed that Antegren reached a maximum serum concentration (Cmax) of approximately 50 microg/ml in roughly 2 h (Tmax), and the half-life was about 4.5 days. Moreover, Antegren could still be detected in circulation 3 to 8 weeks after a single iv dose of 3 mg/kg. In summary, this data justified conducting efficacy studies with Antegren following acute dosing in MS.

Phase II

Multiple sclerosis
Antegren efficacy was assessed in a double-blind study in patients (n = 72) exhibiting either relapsing-remitting, or secondary chronic progressive MS, who were enrolled at eight sites in the UK [**344447**]. Each patient received two iv infusions of either Antegren (3 mg/kg), or placebo separated by a 4-week period. The endpoints of the study were lesion activity in MS measured by magnetic resonance imaging (MRI) scans, and overall clinical evaluation, recorded at 12 and 24 weeks after administering the first dose of Antegren. In the first 12 weeks following initiation of treatment, patients in the Antegren group, exhibited fewer new active lesions compared to placebo. In particular, MRI scans showed that the mean cumulative number of new active lesions was 1.8 for the Antegren cohort versus 3.6 ($p < 0.05$) for placebo. Nevertheless, the total number of exacerbations in the first 12 weeks was not statistically different in the Antegren (n = 9), or placebo group (n = 11). Thus, the data suggest that preservation of blood-brain barrier (BBB) integrity is afforded in the initial 12 weeks after Antegren administration. However, this effect may not be sufficient to have a clinical impact in patients, particularly in terms of MS exacerbations. By week 12, serum titers of Antegren had reached below saturation levels (ie, 1 microg/ml) in the vast majority of treated patients (97%). Consistent with this result, from weeks 12 to 24 after initiation of treatment, the mean cumulative number of new active lesions was not significantly different in the Antegren versus placebo group. Again, this suggests that continuous blockade of alpha4 integrin on lymphocytes is necessary to prevent their entry into the MS brain tissue.

Interestingly, the total number of disease exacerbations was significantly higher in patients treated with Antegren (n = 14) compared to placebo (n = 3, $p < 0.05$), from week 12 to 24 after initiation of treatment. Thus, a 'rebound' effect may be seen in patients receiving Antegren, after the antibody is cleare d from circulation.

Phase II/III

Crohn's disease
In two separate pilot studies, Antegren showed a positive trend towards efficacy in the treatment of patients suffering from Crohn's disease or ulcerative colitis (n = 40) [**275424**]. As with the MS trial, Antegren therapy was well tolerated by these patients [**275424**].

Side Effects and Contraindications

In the phase I trial, three out of six patients in the highest single dose group, ie, 3 mg/kg, developed anti-Antegren or anti-idiotypic antibodies. However, in the phase II study, only a small proportion of patients in the Antegren group (4/37, 11%) generated antibodies to the drug, even though a 3 mg/kg dose was administered twice. In conclusion, while raising anti-drug antibodies is a concern, phase II trial results indicate that it is a relatively infrequent event. Nevertheless, the potential effect of anti-Antegren on MRI scans, or clinical outcomes for the affected patient population was not investigated further.

In the phase II study, patients treated with Antegren experienced lymphocytosis relative to placebo, even though no significant differences in incidence of other adverse events was noted between the two treatment groups. Between weeks 1 and 12 after initial dosing, there was an increase of 56 to 60% in blood lymphocyte counts in the Antegren cohort, relative to placebo. Lymphocyte numbers remained elevated by week 16, but returned to baseline levels, ie, before initiation of Antegren dosing, by weeks 20, and 24. Taken together, these observations underscore the mechanism of action of Antegren, namely, inhibition of lymphocyte migration. On the negative side, however, they also point to a potentially troubling adverse event, ie, lymphocytosis.

Summary Opinion

MS is a chronic neurodegenerative disease with autoimmune characteristics, and multi-factorial causes. While the precise agent(s) that triggers disease onset is unknown, T-lymphocyte infiltration into the brain and spinal cord tissue is a well-accepted cardinal sign of MS. Recently, autoantibodies to proteins in the myelin sheath have also been identified in plaque areas in the CNS of MS patients [**344449**]. Therefore, it appears that both cellular (ie, T-cell), and humoral (ie, antibody) immunity are involved in this demyelinating disease.

Since Antegren is a blocking monoclonal antibody to the alpha4 integrin, one would expect this treatment to prevent T-cell entry into the CNS of MS patients. In fact, this is exactly what the data from a phase II trial of the drug suggests (see above). Moreover, MRI scans of patients treated with Antegren show that fewer new lesions develop in their brains, relative to placebo. While this is potentially a promising result in the long-term, no apparent impact is observed on the number of disease exacerbations in the short-term. Thus, a clear clinical benefit after Antegren therapy still remains to be demonstrated.

A major concern associated with Antegren treatment is its potential effect on normal lymphocyte recirculation through lymph nodes. In addition, the ability of T-cells to mount cellular immune responses to foreign antigens may be affected by the drug, even though no increase in infections was noted in the phase II study. However, the former caveat appears to be justified by the data from the phase II trial, ie, patients receiving Antegren experience a transient lymphocytosis. This observation suggests that the drug may temporarily inhibit T-cell migration into lymphoid tissues. Consequently, the frequency of Antegren therapy may be limited in order to allow a patient's

immune system to restore normal blood home stasis.

A second concern is the apparent increase in acute episodes after the drug falls below saturation levels from the systemic circulation (see above). A potential explanation may be related to the observed lymphocytosis. This could be consistent with data from the phase II study, since rates of new lesion formation were comparable for the placebo an d Antegren groups following drug clearance [344447]. A likely interpretation of this result is that both groups exhibited a similarly compromised BBB, when the alph4 integrin on T-cells was not blocked. Thus, patients receiving Antegren may have more T-cells infiltrating the CNS parenchyma, simply because they have greater numbers in circulation after the drug has been cleared. In turn, this may translate into more clinical exacerbati ns in the drug group shortly after Antegren therapy is discontinued.

In conclusion, Antegren appears to be a "near hit", as an editorial comment accompanying publication of the phase II trial argues [344451], but several questions still remain to be resolved. In the meantime, the sponsor of the drug, Elan Corporation of Ireland, states that development of Antegren as an acute MS therapy will not be further supported, shifting its focus instead to chronic treatment of patients with MS [344452].

Name	Summary	Reference
Biogen Inc	In August 2000, Biogen and Elan announced a worldwide collaboration to develop, magufacture and commercialize Antegren. Costs and benefits will be shared. Financial terms were not disclosed.	379455
Protein Design Labs Inc	In April 1998, Protein Design Labs (PDL) granted a worldwide, nonexclusive license under its antibody humanisation patents to a subsidiary of Elan's for Antegren. Under the terms of the agreement, Elan is paying a non-refundable licensing and signing fee of $1.3 million to PDL and has agreed to make milestone and royalty payments for the licensed product.	286198
Axogen ltd	Codeveloping Antegren for MS as part of a four-drug joint venture with Elan Corp (Athena).	223736

Study Type	Effect Studied	Experimental Model	Result	Reference
In vivo	Reversal of pathology of experimental allergic encephalomyelitis	Experimental allergic encephalomyelitis in guinea pig	Reduction in edema in CNS and blood-brain barrier permeability by AN-100226	222522
In vivo	Reversal of pathological signs associated with experimental allergic encephalomyelitis	Experimental allergic encephalomyelitis in guinea pig	Antibodies against alpha4 beta1 integrin induced a rapid clearance of leukocytes from the CNS and reduction in the pathological features, including demyelination	265842
In vivo	Reversal of pathology associated with experimental allergic encephalomyelitis	Virus-facilitated experimental allergic encephalomyelitis in mice	Antibodies against alpha4beta1 integrin decreased clinical and histopathological signs, including a reduction of VLA4+ cell infiltration and a decreased induction of vascular cell adhesion molecule-1 on brain vessels	265845
In vitro	Lymphocyte and monocyte binding to experimental allergic encephalomyelitis brain vessels	Adhesion assay on tissue sections	Antibodies to alpha 4 beta 1 integrin inhibited adhesion of lymphocytes and monocytes to brain vessels from experimental allergic encephalomyelitis animals	279263

Study Type	Result	Reference
Development of antibody	Humanization of mouse monoclonal antibody against alpha4beta1 integrin, AN-100226m	269705

Study Type	Effect Studied	Experimental Model	Result	Reference
	Antegren effects on new brain lesion information in patients with multiple sclerosis	Phase II double-blind, placebo-controlled, multicenter study in the UK	Antegren on day 0 and day 28 of a 12 week study reduced the number of new brain lesions in patients with multiple sclerosis when compared to placebo	275424
	Effects of Antegren in patients with Crohn's disease or ulcerative colitis	Pilot clinical study	A total of 40 patients given Antegren showed improvement	275424